REMARKS

Formal Matters

Claims 1-43 are pending after entry of the amendments set forth herein.

Claims 27-30 were examined. Claims 27-30 were rejected.

Claims 27-30 are amended and claims 38-43 are new. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to the claims and the new claims is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 5 line 28 and page 8 line 38 to page 9 line 2. Accordingly, no new matter is added by these amendments.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Rejections Under 35 U.S.C. §112, ¶2

Claim 27 is rejected under 35 U.S.C. §112, ¶2 for reciting an abbreviation for a protein "TaHo" without providing an expansion for the same.

Claim 27 is amended to recite "Tankyrase H (TaHo)".

The Applicants respectfully submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Claim 28 is rejected under 35 U.S.C. §112, ¶2 for reciting the phrase "small molecule".

The Applicants respectfully submit that what is meant by a small molecule is described in the specification at page 29, lines 12-21, e.g., small molecules have a molecular weight of between 100 and about 2,500 daltons. In light of the definition of "small molecule" in the specification, the Applicants respectfully submit that a skilled person would understand the metes and bounds of what is meant by the term "small".

The Applicants respectfully submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Rejections Under §112, ¶1 – Enablement

Claims 27-30 are rejected under 35 U.S.C. §112, first paragraph, assertedly because the specification does not provide reasonable enablement for a method using any and all proteins encoded by a polynucleotide that is 90% identical to SEQ ID NO:1 or 2. In making the rejection, the Office Action states that the specification provides reasonable enablement for a method using SEQ ID NO:1 or 2. The Applicants respectfully traverse this rejection.

The Applicants note that new claim 41 is directed to a method involving SEQ ID NO:3 or 4 (i.e., the polypeptides encoded by SEQ ID NOS:1 and 2). As such, this rejection is believed to be moot with respect to claim 42.

New claim 41 recites a method involving a polypeptide that is at least 95% identical to SEQ ID NO:3 or 4 and is also believed to be patentable for the reasons set forth below.

The Office Action appears to base this rejection on the idea that the specification does not give adequate guidance for providing polypeptides having desirable characteristics. The Applicants respectfully disagree.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

The Examiner is respectfully reminded that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims (MPEP §2164.08) and the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled (MPEP §2164.08(b)). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort that is normally required in the art (MPEP §2164.08(b)).

The specification describes the subject molecules has having "PARP", i.e., poly-ADP ribose polymerase, activity. The specification describes two isoforms of Taho having PARP activity (SEQ ID NOS:3 and 4) and describes two different Taho variants that do not have PARP activity (see figure 5). The two isoforms of Taho recited by sequence have a "PARP domain" (see figure 5), which is a well

---

[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

known domain. In fact, a search of Medline using the search strategy ("parp" OR "poly-ADP ribose polymerase") yielded 1561 matches among references published in 1999 alone (the year of the earliest priority application), and, as such, the Applicants respectfully submit that the general state of the art with respect to PARP domain-containing proteins is exceedingly high.

Further, with respect to PARP domain proteins, NCBI's "conserved domain database" indicates that there are at least about 70 examples of eukaryotic PARP domain polypeptides other than the ones provided in SEQ ID NOS:1 and 2 (see Exhibit I). Exhibit J is an alignment of six exemplary eukaryotic PARP domains indicating that some amino acids are highly conserved in the PARP domain, whereas other amino acids are highly variable.

Further, the crystal structure of the catalytic domain of poly(AD-ribose) polymerase is known (e.g. Ruf et al., Proc Natl Acad Sci U S A. 1996 93:7481-5; abstract enclosed as Exhibit K), and the structure/function relationship between the amino acids of PARP domains has been studied extensively (e.g. Uchida et al., Gene. 1993 137:293-7 and Masson, Biochimie. 1995 77:456-61; abstracts enclosed as Exhibits L and M, respectively). In fact, the PARP domain has been extensively mutagenized to reveal particular amino acids of importance for PARP activity (Simonin, J Biol Chem. 1993 268:8529-35 and Rolli, Biochemistry 1997 36:12147-54; abstracts enclosed as Exhibits O and P, respectively).

The Applicants respectfully submit that in view of the above information, a skilled person would know exactly which amino acids of SEQ ID NOS:3 or 4 cannot be changed, and others that could be changed, in order to create a variant that retains PARP activity.

Further, the instant application claims priority to two "parent" applications. The Applicants further note that the first parent of the instant application issued as US patent 6,589,725 and contained claims directed to screening methods involving "a tankyrase H protein, wherein said tankyrase H protein comprises an amino acid sequence having **at least about 95% identity to the amino acid sequence set forth in SEQ ID NO:2**, and wherein said tankyrase H protein has PARP activity". The Applicants also note that the second parent of the instant application is currently in allowance, and screening claims involving a tankyrase H protein, wherein "said tankyrase H cell cycle protein comprises the sequence of SEQ ID NO:3 or an amino acid sequence having **at least about 95% identity to the amino acid sequence set forth in SEQ ID NO:4** and will bind to p21" are allowed.

For the sake of consistency of application of the law of written description during examination of related applications, the instant claims, reciting a **TaHo protein is encoded by a nucleic acid having at**

least 90% identity to SEQ ID NOS:1 or 2 (claim 27), or at least 95% identical to an amino acid sequence set forth in SEQ ID NOS:3 or 4 (claim 41), should also be considered enabled.

In summary, the specification discloses that the instant tankyrase is a PARP domain protein and describes two tankyrase H proteins that have PARP activity and two tankyrase H variants that do not have PARP activity. The level of knowledge of the structure of PARP domain proteins is, in general, extremely high, and, as such, a skilled person, upon viewing the sequence of SEQ ID NOS:3 or 4, would be able to predict, with a high degree of certainty, which amino acids of SEQ ID NOS:3 or 4 could be changed without altering the PARP activity of the polypeptide and practice the claimed subject matter without undue experimentation.

In view of the foregoing discussion, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §112, ¶1 – Written Description

Claims 27-30 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action asserts that the specification provides an inadequate description of the modified polypeptide sequence encompassed by the claims. The Applicants respectfully traverse this rejection.

In making the rejection, the Office Action argues that "The specification does not contain any disclosure of the function of **all** the polypeptide sequence encoded by polynucleotides that are 90% identical to SEQ ID NO:1 or 2, including fragments and variants within the scope of the claimed genus." (emphasis added). Further, the Office Action refers the Applicant to the revised guidelines concerning compliance with the written description requirement of 35 U.S.C. §112, ¶1.

With respect to satisfying the written description requirement, even in an "unpredictable art," applicants "are *not* required to disclose *every* species encompassed by their claims . . . ."[2] Otherwise, to claim a genus, every species within a genus would have to be explicitly described. This is **not** the law. In other words, the written description requirement does not require a specific description of every species encompassed by a claim.

---

[2] *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218, (C.C.P.A. 1976).

As such, the Office's argument that the specification does not contain any disclosure of the function of **all** the polypeptide sequence encoded by polynucleotides that are 90% identical to SEQ ID NO:1 or 2, has no bearing on the instant claims because such a level of disclosure is not required by law.

With respect to the written description guidelines, the guidance set forth in the "Synopsis of Application of Written Description Guidelines", as published to the world wide website of the U.S.P.T.O. on March 1st, 2000 (http://www.uspto.gov/web/offices/pac/writtendesc.pdf), indicates that the claims are adequately described.

Example 14 of the Synopsis describes a scenario that is very similar to that currently under examination. Example 14 provides an example of a specification that discloses the sequence of a polypeptide having the sequence of SEQ ID NO:3, and also discloses that the polypeptide has a certain enzymatic activity. This example also states that the specification also "contemplates but does not exemplify" variants of SEQ ID NO:3, and provides an assay for measuring the activity of the protein. In this example, the claims are directed to polypeptides having a sequence that is at least 95% identical to that of SEQ ID NO: 3 and catalyze the reaction of A→B.

The Synopsis states that the claimed subject matter is adequately described by the specification and the requirements of 35 USC §112 first paragraph have been met because "The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity.

For the Examiner's convenience, Example 14 of the Synopsis of Application of Written Description Guidelines is reproduced below:

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of **A B.** The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:
A protein having SEQ ID NO: 3 and variants thereof that are at least 95%

identical to SEQ ID NO: 3 and catalyze the reaction of A B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3.

Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species.

The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

The Applicants respectfully submit that the fact pattern of the example set forth above is very similar to the instant fact pattern. In other words, the instant specification a) describes the sequence of a full length polypeptides (to be more exact, SEQ ID NO:3, SEQ ID NO:4, and two variants shown in Fig. 5), b) describes that SEQ ID NO:3, SEQ ID NO:4 have PARP activity, c) "contemplate but does not exemplify" variants of SEQ ID NOS:3 and 4, and d) provides detailed methods of how PARP activity can be assayed.

As such, by the reasoning set forth in the Example 14 of the Synopsis, in combination with the vast amount of public knowledge on the structure of PARP proteins (discussed in the "enablement" section above), the instant claims should be considered adequately described by the specification, meeting the requirements of 35 USC §112, first paragraph.

For the sake of consistency of examination between applications, the instant claims, reciting a **TaHo protein is encoded by a nucleic acid having at least 90% identity to SEQ ID NOS:1 or 2 (claim 27), or** at least 95% identical to an amino acid sequence set forth in SEQ ID NOS:3 or 4 (claim 41), should also be considered enabled.

Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(a)/(e)

Claims 27-30 are rejected as being anticipated under 35 U.S.C. §102(a) and (e) by Berthelsen et al. (USPN 6,455,290), which has a filing date of July 9, 1999. This rejection is respectfully traversed.

As set out in 37 C.F.R. §1.131:

> (a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§1.42, 1.43, or 1.47, ***may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference*** or activity on which the rejection is based. . . .
>
> (b) ***The showing of facts shall be such, in character and weight, as to establish*** reduction to practice prior to the effective date of the reference, ***or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application***. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence satisfactorily explained.
> (emphasis added)

The Applicants note that PARP activity assays are described in this parent of the instant application, on page 30, line 32 to page 31 line 2. As such, a §102(a) or §102(e) rejection may be withdrawn if the Applicants establish, by means of a declaration and a showing of facts, that the claimed subject matter was conceived prior to July 9, 1999 (Berthelsen's filing date), and diligently reduced to practice from the period between July 9, 1999 and October 25, 1999, the filing date of a parent of the instant application.

In order to establish that the claimed invention was conceived prior to July 9, 1999, and diligently reduced to practice from the period between July 9, 1999 and October 25, 1999, the Applicants submit herewith the Declaration of Dr. Yasumichi Hitoshi under 37 C.F.R. §1.131.

The Applicants respectfully submit that Dr. Hitoshi's declaration and attached exhibits demonstrate conception of the claimed subject matter prior to July 9, 1999, and diligent reduction to practice between July 9, 1999 and October 25, 1999 for the following reason:

Exhibits A and B, dated prior to July 9, 1999, demonstrate that the Inventors had identified the sequence of the PARP domain of Tankyrase H, and identified that Tankyrase H had PARP activity. The Applicants respectfully submit that Exhibits A and B demonstrate that the Inventors had conceived the subject matter of the rejected claims prior to July 9, 1999.

Exhibit C sets forth a detailed description of experiments for identifying the full length sequence of Tankyrase H for use in the claimed screening assays. The Applicants respectfully submit that Exhibit C, showing the following dates: July 9, July 13, July 15, July 16 and July 21, 1999, demonstrates that the Inventors diligently worked towards the subject matter of the rejected claims between July 9 and July 21, 1999.

Exhibits D - H represent correspondence between Rigel (the assignee of the above-referenced patent application) and Rigel's patent counsel with regard to drafting of the above referenced patent application. Exhibits D – H show the following dates: July 20, July 22, July 26, August 20, August 26, August 30, and September 30, 1999. The Applicants respectfully submit that this correspondence demonstrates that Rigel's patent counsel diligently worked on the above-referenced patent application between July 20, 1999 and its filing date October 25, 1999.

As such, since the filing date of a patent application may represent a constructive reduction to practice (see, e.g., MPEP § 2138.05), the Applicants respectfully submit that they conceived of the invention prior to the effective date of Berthelsen (July 9, 1999) and diligently worked towards a

reduction to practice of the invention between July 9, 1999 and October 25, 1999, the filing date of the instant patent application.

Accordingly, since the Applicants have provided an appropriate declaration and showing of facts that establish conception of the invention prior to the effective date of Berthelsen coupled with due diligence from prior to Berthelsen's effective date to filing of the application, this rejection this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RIGL-010CIP2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 09-16-2003

By: James S Keddie
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Enclosures: Declaration of Yasumichi Hitoshi Under 37 C.F.R. §1.131
Exhibits A-H (attached to the declaration)
Exhibits I-P (attached to the response)

F:\DOCUMENT\RIGL (Rigel)\010CIP2\response to OA dated April 16, 2003.doc